

Growth Factors, Nutrients and Cancer

Junior Group

Summary

Deciphering the nutrient and growth factor signalling cascades is at the root of understanding how cellular economy is regulated. We have reported the identification of a novel downstream effector of mTOR-S6K1 mitochondria pathway, termed URI. URI functions by binding to and inhibiting mitochondria-resident PP1 γ , to ensure fine tuning of the apoptotic threshold in accordance with nutrient and growth factor availability. Using live cell imaging technology, we intend to define molecular mechanisms explaining why cancer cells are resistant to apoptosis. In parallel, the use of mouse models will help to understand the contribution of nutrients and growth factors to cancer development.

Strategic Goals

- Identify upstream signalling components integrating nutrients and growth factors
- Elucidate signalling pathways and mechanisms regulating URI function in response to metabolic stress
- Define the functions of the URI/ PP1 γ complex by coordinating cell metabolism and survival at the mitochondria
- Analyse potential oncogenic properties of URI using mouse models in collaboration with Erwin Wagner from the BBVA Foundation - CNIO Cancer Cell Biology Programme
- Crystallise the URI/PP1 γ complex in collaboration with the CNIO Macromolecular Crystallography Group

Nabil Djouder *Junior Group Leader (since September)*



Nabil Djouder obtained his PhD in Molecular Pharmacology from the University of Strasbourg (France) and the University of Freiburg (Germany), where he worked in the laboratory of K. Aktories. He studied the molecular mechanisms underlying the activation of mast cells by the cross-linking of high affinity antigen receptors (Fc ϵ -RI) and the involvement of small GTPases from the Rho family in this activation.

In 2001 he moved to Basel (Switzerland) as a postdoctoral research fellow and joined the laboratory of W. Krek at the Novartis Friedrich Miescher Institute. He has since been working in the fields of growth control, cancer, and associated metabolic disorders. Most of his research focuses on the mTOR/S6K pathway and the integration of growth factors, nutrients, and energy homeostasis. He established URI and PP1 γ as new mitochondrial components, integrating a previously unrecognised S6K1-regulated mitochondrial pathway dedicated, in part, to oppose sustained S6K1 survival signalling and ensuring that the mitochondrial threshold for apoptosis is set in accord with nutrient and growth factor availability.

In 2003 he moved with W. Krek to the Institute of Cell Biology at the *Eidgenössische Technische Hochschule* (ETH) in Zurich. He accepted the challenge of becoming a member of the Competence Centre for Systems Physiology and Metabolic Diseases (CCSPM) that converts systems biology into physiology and medicine.

In September 2009 Nabil Djouder joined the BBVA Foundation - CNIO Cancer Cell Biology Programme as Junior Group Leader, establishing his Group in the field of growth factors, metabolism, and cancer.



Graduate student: Krishna S. Tummala.

Highlights

URI in growth factor and nutrient circuitry: The integration of growth factor and nutrient signals converges on mTOR/S6K1 pathways, which in coordination control cellular growth and survival (Figure 1). The survival function of S6K1 is mediated, at least in part, as a mitochondria-bound enzyme that phosphorylates the death agonist BAD at Ser-136 in response to insulin-like growth factor 1 (IGF1) (Figure 1). The dual capacity of S6K1 to promote cell growth and cell survival therefore suggests the existence of specific mechanisms that regulate S6K1 activity and couple S6K1 downstream signalling to changes in nutrient and growth factor signals. In this respect, we recently identified an evolutionarily conserved and unconventional member of the prefoldin (PFD) family of molecular chaperones, termed URI (for Unconventional prefoldin RPB5 Interactor). Existing evidence suggests a tight correlation between URI phosphorylation and mTOR activity.

We report that URI represents a novel substrate of S6K1 *in vivo*. In growth factor-deprived or rapamycin-treated cells, URI forms stable complexes with protein phosphatase (PP1) γ at mitochondria, thereby inhibiting phosphatase activity. Growth factor stimulation induces disassembly of URI/PP1 γ complexes through S6K1-mediated phosphorylation of URI at serine 371 and the subsequent activation of a PP1 γ -dependent negative feedback programme. This activation results in diminished S6K1 activity and BAD phosphorylation as well as an enhanced sensitivity of cells to BAD-dependent apoptosis.

These findings establish that URI and PP1 γ are integral components of a previously unrecognised S6K1-regulated mitochondrial pathway dedicated, at least in part, to opposing sustained S6K1 survival signalling, thereby ensuring that the mitochondrial threshold for apoptosis is set up in accordance with nutrient and growth factor availability.

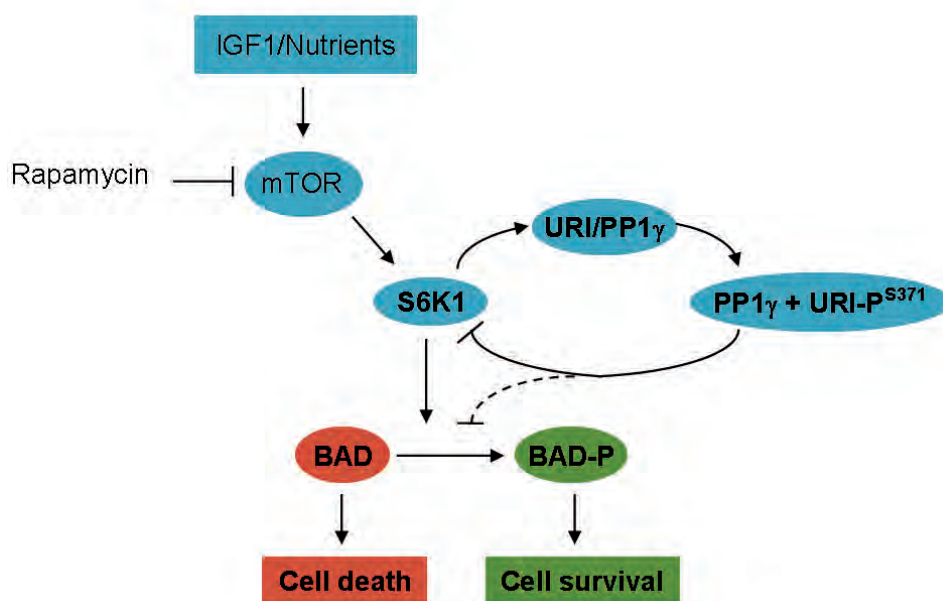


Figure: Model proposing a role for URI and PP1 γ as central components of a negative feedback mechanism that counteracts S6K1 survival signalling to BAD in response to growth factors.